

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method for identifying display molecule(s) having affinity towards molecular target(s), comprising the steps of

providing one or more target complexes, each comprising a molecular target associated with a target oligonucleotide,

providing a library of bifunctional complexes, each bifunctional complex of the library comprising a display molecule attached to an identifier oligonucleotide that codes for said display molecule,

mixing said one or more target complexes with said library of bifunctional complexes, so that said bifunctional complexes may bind to one or more of said target complexes, by virtue of interaction between the display molecule of said bifunctional complex and the target of said target complex,

covalently coupling the target oligonucleotide[[.]] of a target complex bound to a bifunctional complex, with the identifier oligonucleotide of said bifunctional complex, said coupling being in addition to the indirect coupling resulting from said binding of the display molecule to the target, and

deducing the identity of the binding display molecule(s) and/or the molecular target(s) from the coupled product between the identifier oligonucleotide(s) and the target oligonucleotide(s).

2. (Original) The method of claim 1, wherein the display molecule is a reaction product of two or more chemical entities and the identifier oligonucleotide comprises codons identifying the chemical entities.

3. (Original) The method of claim 1, wherein one or more members of the library are potentially binding compounds tagged with identifier oligonucleotides.
4. (Previously Presented) The method according to claim 2, wherein the chemical entities are precursors for a structural unit appearing in the display molecule.
5. (Previously Presented) The method according to claim 2, wherein some or all of the chemical entities are not naturally occurring α -amino acids or precursors thereof.
6. (Previously Presented) The method according to claim 2, wherein each codon comprises 4 or more nucleotides.
7. (Previously Presented) The method according to claim 1, wherein the display molecules of the library complexes are non- α -polypeptides.
8. (Previously Presented) The method according to claim 1, wherein the display molecules of the library complexes are non-nucleic acids.
9. (Previously Presented) The method according to claim 1, wherein the display molecule has a molecular weight less than 2000 Dalton.
10. (Previously Presented) The method according to claim 1, wherein the identifier oligonucleotide uniquely identifies the display molecule.
11. (Previously Presented) The method according to claim 2, wherein the display molecule is formed by the reaction of a nascent display molecule with one or more chemical entities, said nascent display molecule itself being the reaction product of two or more chemical entities, and one or more chemical entities are transferred to the nascent display molecule by a chemical building block further comprising an anti-codon.

12. (Previously Presented) The method according to claim 11, wherein the bifunctional complex is formed by the reaction(s) of a nascent complex, comprising a nascent display molecule and a nascent identifier oligonucleotide, with one or more chemical entities and the same number of codons identifying the chemical entities, and an anti-codon is transferred in conjunction with the chemical entity to the nascent complex.

13. (Previously Presented) The method according to claim 2, wherein the chemical entities are reacted without enzymatic interaction.

14. (Previously Presented) The method according to claim 2, wherein the codons are separated by a framing sequence.

15. (Previously Presented) The method according to claim 1, wherein the display molecule and the identifier oligonucleotide are joined by a selectively cleavable linker.

16. (Original) The method according to claim 15, wherein the linker is cleaved by irradiation.

17. (Canceled)

18. (Previously Presented) The method according to claim 1, wherein the library comprises 1,000 or more different complexes.

19. (Original) The method according to claim 1, wherein the molecular target is of a biological origin.

20. (Previously Presented) The method according to claim 1, wherein the molecular target is immobilized on a solid support.

21-68 (Canceled).

69 (Withdrawn) A method for generating a conjugate comprising a molecular target associated with a target oligonucleotide and a bifunctional complex comprising a display molecule attached to an identifier oligonucleotide which codes for said display molecule,

wherein said display molecule has an affinity for and is bound to said molecular target,

said method comprising the steps of

- i) providing a target scaffold chemical unit having one or more reactive groups,
- ii) providing a first chemical entity comprising a reactive group,
- iii) providing an oligonucleotide tag identifying the first chemical entity provided in step ii),
- iv) providing at least a second chemical entity comprising a reactive group,
- v) providing an oligonucleotide tag identifying said at least second chemical entity,
- vi) generating a molecular target associated with a target identifier oligonucleotide by reacting

in a first reaction step a)

the scaffold chemical unit provided in step i) and the reactive group of the first chemical entity provided in step ii), thereby generating an addition to the target scaffold chemical unit, by reacting

in a second reaction step b)

the reactive group of at least a second chemical entity and the target scaffold chemical unit, or

the reactive group of at least a second chemical entity and the addition to the target scaffold chemical unit obtained in reaction step a), and by appending in further reaction steps

oligonucleotide tags identifying said first chemical entity and said at least second chemical entity, respectively, to the reaction product obtained from the reaction of the scaffold chemical unit, the first chemical entity and the at least second chemical entity,

wherein said first chemical entity and said at least second chemical entity are identified by said target identifier oligonucleotide comprising tags identifying said first chemical entity and said at least second chemical entity,

- vii) providing a display molecule scaffold chemical unit having one or more reactive groups,
- viii) providing a further first chemical entity comprising a reactive group,
- ix) providing an oligonucleotide tag identifying the further first chemical entity provided in step viii),
- x) providing at least a further second chemical entity comprising a reactive group,
- xi) providing an oligonucleotide tag identifying said at least further second chemical entity,

- xii) generating a display molecule associated with a display molecule identifier oligonucleotide by reacting

in a first reaction step c)

the display molecule scaffold chemical unit provided in step vii) and the reactive group of the further first chemical entity provided in step viii), thereby generating an addition to the display molecule scaffold chemical unit; by reacting

in a second reaction step d)

the reactive group of at least a further second chemical entity and the display scaffold chemical unit, or

the reactive group of at least a further second chemical entity and the addition to the display scaffold chemical unit obtained in reaction step c), and by appending

in further reaction steps

oligonucleotide tags identifying said further first chemical entity and said at least further second chemical entity, respectively, to the reaction product obtained from the reaction of the display molecule scaffold chemical unit, the further first chemical entity and the further second chemical entity,

wherein said further first chemical entity and said at least further second chemical entity are identified by said display molecule identifier

oligonucleotide comprising tags identifying said further first chemical entity and said at least further second chemical entity,

xiii) reacting in a yet further reaction step e)

the molecular target associated with a target identifier oligonucleotide as generated in step vi) and the display molecule associated with a display molecule identifier oligonucleotide as generated in step xii), thereby generating a conjugate comprising a molecular target display molecule reaction product,

xiv) coupling the molecular target identifier oligonucleotide and the display molecule identifier oligonucleotide,

xv) optionally extending and/or amplifying said coupling of said molecular target identifier oligonucleotide and said display molecule identifier oligonucleotide, and

xvi) decoding said coupling of said molecular target identifier oligonucleotide and said display molecule identifier oligonucleotide, or a part thereof, thereby identifying the scaffold chemical units and the chemical entities which have participated in the synthesis of the molecular target and/or the display molecule.

70 (Withdrawn) A method for generating a complex comprising a molecular target and a final display molecule comprising more than one molecular part, wherein said final display molecule is attached to identifier oligonucleotides identifying the individual molecular parts of the final display molecule,

wherein said final display molecule has an affinity for and is bound to said molecular target,
said method comprising the steps of

- i) providing a molecular target,
- ii) providing a first display molecule scaffold chemical unit,
- iii) providing a first chemical entity comprising a reactive group,
- iv) providing an oligonucleotide tag identifying the first chemical entity provided in step ii),
- v) providing at least a second chemical entity comprising a reactive group,
- vi) providing oligonucleotide tags identifying said at least second chemical entity,
- vii) generating a first display molecule associated with a first identifier oligonucleotide
by reacting in a first reaction step a)

the first display molecule scaffold chemical unit provided in step ii) and the reactive group of the first chemical entity provided in step iii), thereby generating an addition to the scaffold chemical unit,

by reacting in a second reaction step b)

the reactive group of at least a second chemical entity and the first scaffold chemical unit, or

the reactive group of at least a second chemical entity and the addition to the first scaffold chemical unit obtained in reaction step a), and

by appending in further reaction steps

oligonucleotide tags identifying said first chemical entity and said at least second chemical entity, respectively, to the reaction product obtained from the reaction of the scaffold chemical unit, the first chemical entity and the second chemical entity,

wherein said first chemical entity and said at least second chemical entity are identified by said first identifier oligonucleotide comprising tags identifying said first chemical entity and said at least second chemical entity,

- viii) providing a second display molecule scaffold chemical unit having one or more reactive groups,
 - ix) providing a further first chemical entity comprising a reactive group,
 - x) providing an oligonucleotide tag identifying the further first chemical entity provided in step ix),
 - xi) providing at least a further second chemical entity comprising a reactive group,
 - xii) providing an oligonucleotide tag identifying said at least further second chemical entity,
 - xiii) generating a second display molecule associated with a second display molecule identifier oligonucleotide
- by reacting in a further first reaction step c)

the second display molecule scaffold chemical unit provided in step viii) and the reactive group of the further first chemical entity provided in step ix), thereby generating an addition to the second display molecule scaffold chemical unit;

by reacting in a further second reaction step d)

the reactive group of at least a further second chemical entity and the display scaffold chemical unit, or

the reactive group of at least a further second chemical entity and the addition to the second display molecule scaffold chemical unit obtained in reaction step c), and

by appending in further reaction steps

oligonucleotide tags identifying said further first chemical entity and said at least further second chemical entity, respectively, to the reaction product obtained from the reaction of the second display molecule scaffold chemical unit, the further first chemical entity and the further second chemical entity,

wherein said further first chemical entity and said at least further second chemical entity are identified by said second display molecule identifier oligonucleotide comprising tags identifying said further first chemical entity and said at least further second chemical entity,

xiv) reacting in a yet further reaction step e)

the first display molecule associated with a first display molecule identifier oligonucleotide as generated in step vii) and the second display molecule associated

with the second display molecule identifier oligonucleotide as generated in step xiii), thereby generating a final display molecule,

xv) reacting in a still further reaction step f)

the final display molecule and a molecular target, thereby generating a complex comprising a molecular target and a final display molecule comprising more than one molecular part, wherein said final display molecule is attached to identifier oligonucleotides identifying the individual molecular parts of the final display molecule,

xvi) coupling the first display molecule identifier oligonucleotide and the second display molecule identifier oligonucleotide,

xvii) optionally extending and/or amplifying said coupling of said first display molecule identifier oligonucleotide and said second display molecule identifier oligonucleotide, and

xviii) decoding said coupling of said first display molecule identifier oligonucleotide and said second display molecule identifier oligonucleotide, or a part thereof, thereby identifying the chemical entities which have participated in the synthesis of the final display molecule.

71 (Withdrawn) A method for generating a second generation library comprising a molecular target associated with a target oligonucleotide and a bifunctional complex comprising a modified display molecule attached to an identifier oligonucleotide which codes for said modified display molecule,

wherein said modified display molecule has an affinity for and is bound to said molecular target,

said method comprising the steps of

- i) providing a target scaffold chemical unit having one or more reactive groups,
- ii) providing a first chemical entity comprising a reactive group,
- iii) providing an oligonucleotide tag identifying the first chemical entity provided in step ii),
- iv) providing at least a second chemical entity comprising a reactive group,
- v) providing oligonucleotide tags identifying said at least second chemical entity,
- vi) generating a molecular target associated with a target identifier oligonucleotide by reacting

in a first reaction step a)

the scaffold chemical unit provided in step i) and the reactive group of the first chemical entity provided in step ii), thereby generating an addition to the target scaffold chemical unit, by reacting

in a second reaction step b)

the reactive group of at least a second chemical entity and the target scaffold chemical unit, or

the reactive group of at least a second chemical entity and the addition to the target scaffold chemical unit obtained in reaction step a), and by appending

in further reaction steps

oligonucleotide tags identifying said first chemical entity and said at least second chemical entity, respectively, to the reaction product obtained from the reaction of the scaffold chemical unit, the first chemical entity and the at least second chemical entity,

wherein said first chemical entity and said at least second chemical entity are identified by said target identifier oligonucleotide comprising tags identifying said first chemical entity and said at least second chemical entity,

- vii) providing a display molecule scaffold chemical unit having one or more reactive groups,
 - viii) providing a further first chemical entity comprising a reactive group,
 - ix) providing an oligonucleotide tag identifying the further first chemical entity provided in step viii),
 - x) providing at least a further second chemical entity comprising a reactive group,
 - xi) providing an oligonucleotide tag identifying said at least further second chemical entity,
 - xii) generating a display molecule associated with a display molecule identifier oligonucleotide by reacting
- in a first reaction step c)

the display molecule scaffold chemical unit provided in step vii) and the reactive group of the further first chemical entity provided in step viii), thereby generating an addition to the display molecule scaffold chemical unit; by reacting

in a second reaction step d)

the reactive group of at least a further second chemical entity and the display scaffold chemical unit, or

the reactive group of at least a further second chemical entity and the addition to the display scaffold chemical unit obtained in reaction step c), and by appending

in further reaction steps

oligonucleotide tags identifying said further first chemical entity and said at least further second chemical entity, respectively, to the reaction product obtained from the reaction of the display molecule scaffold chemical unit, the further first chemical entity and the further second chemical entity,

wherein said further first chemical entity and said at least further second chemical entity are identified by said display molecule identifier oligonucleotide comprising tags identifying said further first chemical entity and said at least further second chemical entity,

xiii) reacting in a yet further reaction step e)

the molecular target associated with a target identifier oligonucleotide as generated in step vi) and the display molecule associated with a display molecule identifier

oligonucleotide as generated in step xii), thereby generating a conjugate comprising a molecular target display molecule reaction product,

- xiv) separating from said conjugate said display molecule associated with a display molecule identifier oligonucleotide having in step xiii) reacted with said molecular target associated with a target identifier oligonucleotide to generate a conjugate comprising a molecular target display molecule reaction product,
- xv) modifying said display molecule associated with a display molecule identifier oligonucleotide having in step xiv) been separated, said modification comprising
 - a. adding to said display molecule a further component in the form of a chemical entity and/or a structural unit, or
 - b. subtracting from said display molecule a component in the form of a chemical entity and/or a structural unit, or
 - c. reacting said display molecule with a free reactant,

thereby generating a modified display molecule associated with a display molecule identifier oligonucleotide

- xvi) reacting in a further reaction step f)

f) the molecular target associated with a target identifier oligonucleotide as generated in step vi) and the modified display molecule associated with a display molecule identifier oligonucleotide generated in step xv), thereby generating an enriched library comprising conjugates comprising a molecular target modified display molecule reaction product,

xvii) coupling the molecular target identifier oligonucleotide and the display molecule identifier oligonucleotide,

xviii) optionally extending and/or amplifying said coupling of said molecular target identifier oligonucleotide and said display molecule identifier oligonucleotide, and

xix) decoding said coupling of said molecular target identifier oligonucleotide and said display molecule identifier oligonucleotide, or a part thereof, thereby identifying the scaffold chemical units and the chemical entities which have participated in the synthesis of the molecular target and/or the display molecule.

72 (Withdrawn) A method for second generation library driven proximity selection comprising the steps of

- i) generation of a first library,
- ii) generation of a second generation library based on the knowledge obtained from use of said first library, and
- iii) use of said second generation library for proximity selection,

and thereby performing second generation library driven proximity selection;

wherein the generation of the first library comprises the steps of

- a. linking a molecular target to a target oligonucleotide, said target oligonucleotide being unique for the target molecule,
- b. mixing a bifunctional complex comprising a displayed molecule and an identifier oligonucleotide with said molecular target linked to said target

oligonucleotide,

- c. interacting said molecular target with said displayed molecule bringing said molecular target and said target sequence in close proximity with said identifier oligonucleotide,
- d. ligation of said target sequence with said identifier oligonucleotide to generate a ligated product,
- e. amplification of said ligated product using two primers that only amplify ligated products, and
- f. selection of ligated products that contain display molecules that possess affinity for the target molecule.

73 (Withdrawn) A method for second generation library driven proximity selection comprising the steps of

- i) generation of a first library,
- ii) generation of a second generation library based on the knowledge obtained from use of said first library, and
- iii) use of said second generation library for proximity selection,

and thereby performing second generation library driven proximity selection;

wherein the use of the first library is use of a method identifying display molecule(s) having affinity towards molecular target(s), comprising the steps of

- a. mixing one or more molecular target(s) associated with target oligonucleotide(s) and a library of bifunctional complexes, each bifunctional complex of the library comprising a display molecule attached to an identifier oligonucleotide, which codes for said display molecule,
- b. coupling to the target oligonucleotide(s) the identifier oligonucleotide of complexes comprising display molecules binding to the target, and
- c. deducing the identity of the binding display molecule(s) and/or the molecular target(s) from the coupled product between the identifier oligonucleotide(s) and the target oligonucleotide(s).

74 (Withdrawn) A method for generating a complex comprising a molecular target, a first display molecule, and a second display molecule, wherein said first display molecule is attached to an identifier oligonucleotide identifying the first display molecule, and wherein said second display molecule is attached to an identifier oligonucleotide identifying the second display molecule,

wherein said first and second display molecules have affinity for and are bound to said molecular target,

said method comprising the steps of

- i) providing a molecular target comprising a first target domain and a second target domain,
- ii) providing a first display molecule scaffold chemical unit,
- iii) providing a first chemical entity comprising a reactive group,
- iv) providing an oligonucleotide tag identifying the first chemical entity provided in step

- ii),
 - v) providing at least a second chemical entity comprising a reactive group,
 - vi) providing oligonucleotide tags identifying said at least second chemical entity,
 - vii) generating a first display molecule associated with a first display molecule identifier oligonucleotide
- by reacting in a first reaction step a)
- the first display molecule scaffold chemical unit provided in step ii) and the reactive group of the first chemical entity provided in step iii), thereby generating an addition to the scaffold chemical unit,
- by reacting in a second reaction step b)
- the reactive group of at least a second chemical entity and the first scaffold chemical unit, or
- the reactive group of at least a second chemical entity and the addition to the first scaffold chemical unit obtained in reaction step a), and
- by appending in further reaction steps
- oligonucleotide tags identifying said first chemical entity and said at least second chemical entity, respectively, to the reaction product obtained from the reaction of the scaffold chemical unit, the first chemical entity and the second chemical entity,

wherein said first chemical entity and said at least second chemical entity are identified by said first display molecule identifier oligonucleotide comprising tags identifying said first chemical entity and said at least second chemical entity,

- viii) providing a second display molecule scaffold chemical unit having one or more reactive groups,
- ix) providing a further first chemical entity comprising a reactive group,
- x) providing an oligonucleotide tag identifying the further first chemical entity provided in step ix),
- xi) providing at least a further second chemical entity comprising a reactive group,
- xii) providing an oligonucleotide tag identifying said at least further second chemical entity,
- xiii) generating a second display molecule associated with a second display molecule identifier oligonucleotide

by reacting in a further first reaction step c)

the second display molecule scaffold chemical unit provided in step viii) and the reactive group of the further first chemical entity provided in step ix), thereby generating an addition to the second display molecule scaffold chemical unit;

by reacting in a further second reaction step d)

the reactive group of at least a further second chemical entity and the display scaffold chemical unit, or

the reactive group of at least a further second chemical entity and the addition to the second display molecule scaffold chemical unit obtained in reaction step c), and

by appending in further reaction steps

oligonucleotide tags identifying said further first chemical entity and said at least further second chemical entity, respectively, to the reaction product obtained from the reaction of the second display molecule scaffold chemical unit, the further first chemical entity and the further second chemical entity,

wherein said further first chemical entity and said at least further second chemical entity are identified by said second display molecule identifier oligonucleotide comprising tags identifying said further first chemical entity and said at least further second chemical entity,

xiv) reacting in a yet further reaction step e)

the first display molecule associated with a first display molecule identifier oligonucleotide as generated in step vii) and said first domain of said molecular target, and

the second display molecule associated with the second display molecule identifier oligonucleotide as generated in step xiii) and said second domain of said molecular target,

thereby generating a complex comprising a molecular target comprising a first target domain associated with a first display molecule associated with a first display molecule identifier oligonucleotide, and a second target domain associated with a

second display molecule associated with the second display molecule identifier oligonucleotide,

wherein said first display molecule is attached to an identifier oligonucleotide identifying the first display molecule, and wherein said second display molecule is attached to an identifier oligonucleotide identifying the second display molecule,

- xv) coupling the first display molecule identifier oligonucleotide and the second display molecule identifier oligonucleotide,
- xvi) optionally extending and/or amplifying said coupling of said first display molecule identifier oligonucleotide and said second display molecule identifier oligonucleotide, and
- xvii) decoding said coupling of said first display molecule identifier oligonucleotide and said second display molecule identifier oligonucleotide, or a part thereof, thereby identifying the chemical entities which have participated in the synthesis of the final display molecule.

75 (Withdrawn) A conjugate comprising a molecular target associated with an oligonucleotide and a bifunctional complex comprising a display molecule attached to an identifier oligonucleotide which codes for said display molecule, wherein said display molecule has binding affinity towards said molecular target and is bound thereto.

76 (Canceled)

77 (Withdrawn) The conjugate according to claim 75, wherein the target oligonucleotide and/or the identifier oligonucleotide are joined to the molecular target and/or the display molecule, respectively, through a selectively cleavable link.

78 (Withdrawn) The conjugate according to any of the claim 75, wherein the target oligonucleotide is coupled to the identifier oligonucleotide.

79 (Withdrawn) The conjugate according to claim 78, wherein the coupled oligonucleotide is amplifiable.

80 (Withdrawn) The method according to claim 69, wherein the display molecules of the library complexes are non-nucleic acids.

81 (Withdrawn) The method according to claim 69, wherein each display molecule has a molecular weight less than 2000 Dalton.

82 (Withdrawn) The method according to claim 69, wherein the codons are separated by a framing sequence, wherein said framing sequence positions the reaction of a chemical entity in the synthesis history of the encoded molecule.

83 (Previously Presented) The method according to claim 1, wherein the display molecule has a molecular weight less than 1000 Dalton.

84 (Previously Presented) The method according to claim 1, wherein the display molecule has a molecular weight less than 500 Dalton.

85 (Withdrawn) The method according to claim 1, wherein the target oligonucleotide and the identifier oligonucleotide are coupled to each other by hybridization of portions thereof to each other or to a complementary oligonucleotide.

86 (Withdrawn) The method according to claim 1, wherein the target oligonucleotide and the identifier oligonucleotide are coupled to by chemical means to obtain a covalent conjugate.

87 (Previously Presented) The method according to claim 1, wherein the target oligonucleotide and the identifier oligonucleotide are coupled by enzymatic means to obtain a covalent conjugate.

88 (Previously Presented) The method according to claim 1, wherein at least two different targets are provided, and the target oligonucleotide associated with a particular target identifies that target.

89 (Withdrawn) The method according to claim 85, wherein the target oligonucleotide and the identifier oligonucleotide partly or fully are hybridised to a complementing oligonucleotide.

90 (Previously Presented) The method according to claim 87, wherein the enzymatic means are selected from enzymes of the type polymerase, ligase and restriction enzyme, and any combination thereof.

91 (Previously Presented) The method according to claim 90, wherein a ligase is used to join the target oligonucleotide and the identifier oligonucleotide together.

92 (Previously Presented) The method of claim 91, wherein a connector oligonucleotide having a region complementing a distal part of the target oligonucleotide and a region complementing a distal part of the identifier oligonucleotide is used during the coupling step so as to allow a ligase or a combination of a ligase and a polymerase to join the identifier and target oligonucleotides together.

93. (Withdrawn) The method according to claim 85, wherein a region at the distal ends of the target and identifier oligonucleotides are complementary to each other and a polymerase is allowed to extend the target and/or the identifier oligonucleotide.

94. (Previously Presented) The method according to claim 1, wherein the target oligonucleotide and/or the identifier oligonucleotide is provided with a sticky end to allow a ligase or a polymerase or a mixture thereof to join the oligonucleotides.

95 (Previously Presented) The method according to claim 1, wherein the target and the identifier oligonucleotide or sequences complementary thereto at the proximal end is provided with a priming site.

96 (Previously Presented) The method according to claim 1, wherein the coupled oligonucleotide is amplified by PCR using priming sites positioned proximal to the display molecule and the molecular target, respectively.

97 (Previously Presented) The method according to claim 1, wherein the coupled oligonucleotide is recovered and subjected to amplification.